PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	15 June 2005 (15-06-2005)
Applicant's or agent's file reference 913453-58PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000250	07 February 2005 (07-02-2005)	06 February 2004 (06-02-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC[7]: C07H-21/00, C12Q-1/68, C07H-21/04

Applicant
CANADIAN BLOOD SERVICES ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	13 June 2005 (13-06-2005)	Nathalie Chartrand (819) 994-2341

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [X] on paper

      [X] in electronic form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [ ] filed together with the international application in electronic form

      [X] furnished subsequently to this Authority for the purposes of search.

3 [X] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

The electronic form of the sequence listing was not provided at filing, therefore, the search of the nucleotide sequences of the invention is based on the sequences found in Tables 1 and 2 which correspond to SEQ ID NOs 1 to 36.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	6, 7, 13 to 27, 34 to 39, 43 and 44	YES
	Claims	1 to 5, 8 to 12, 28 to 33, 40 to 42 and 45	NO
Inventive step (IS)	Claims	None	YES
	Claims	1 to 45	NO
Industrial applicability (IA)	Claims	1 to 45	YES
	Claims	None	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 01/32702 A2 (DRK BLUTSPENDEDIENST BADEN-WUERTTEMBERG GMBH [DE/DE]) 10 May, 2001.
(See PCR primers ga41, ga42 and re84 and pages 56 and 57)

D2: WO 00/20634 A1 (NOVA MOLECULAR, INC. [CA/CA] Montreal, Quebec) 13 April, 2000.
(See PCR primer Pla 2-1 for human GPIIIa allele)

D3: WO 02/068684 A2 (PYROSEQUENCING AB [SE/SE] Uppsala (SE) or in US Lunderberg, J. [SE/SE] Stockholm (SE)) 6 September, 2002. (See pages 4 to 6, Example 2)

D4: WO 02/30950 A2 (GENAISSANCE PHARMACEUTICALS, INC. [US/US] New Haven CT) 18 April, 2002
(See page 19, lines 19-29)

D5: HIRSCHHORN, J. N. et al., "SBE-TAGS: An array-based method for efficient single-nucleotide polymorphism genotyping", Proceedings of the National Academy of Sciences of USA, August 2000, Vol. 97, no. 22, pages 12164-12169.

D6: GRAF, S. et al., "Genotyping of HPA-1 (Human Platelet Antigen 1) by mini-sequencing", Blood. 16 November, 2000, Vol. 96, no. 11, Part 2, page 53b.

D7: GASSNER, C. et al., "RHD/CE typing by polymerase chain reaction using sequence-specific primers", Transfusion. October 1997, Vol. 37, pages 1020-1026.

NOVELTY:

Document D1 discloses methods to genotype RHD alleles. These methods simultaneously analyze a plurality of polymorphisms which comprise a step of multiplexing PCR amplification. Also, this reference discloses PCR primers, namely, ga41, ga42 and re84 which are substantially identical to the primers SEQ ID NOs 2, 1 and 4, respectively, of the present application. The teaching of this reference falls within the scope of claims 1 to 5, 8 to 10, 12, 28 to 33, 40 to 42 and 45. Therefore, claims 1 to 5, 8 to 10, 12, 28 to 33, 40 to 42 and 45 do not comply with Article 33(2) of the PCT in view of D1.

Document D2 discloses a primer Pla2-1 used in a method to determine the presence of a variant GPIIIa. This primer is substantially identical to the primer having SEQ ID NO 24 of the present application. The primer of document D2 falls within the scope of claims 1 to 5, 8 to 12 and 40. Therefore these claims do not comply with Article 33(2) of the PCT in view of D2.

Continued on supplemental sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 4, 9, 12, 14, 17, 33, 40 and 41 are indefinite and do not comply with Article 6 of the PCT. The primers of claims 4, 9, 12, 17 and 40, the primers used in the multiplex amplification step of claim 14 and the primers used in the single-base pair primer extension step of claims 33 and 41 are not adequately defined. Polynucleotides are chemical compounds and should be defined in terms of their structural formula (nucleotide sequence) which serve to uniquely and unambiguously distinguish the polynucleotide from all other polynucleotides.

Claims 14, 33 and 41 are indefinite, broader in scope than the teaching of the description and do not comply with Article 6 of the PCT. The method of claims 14 and 41 do not specify which antigens are analyzed and the method of claim 33 does not specify which SNP genotypes are analyzed. Also, the applicant has not described the use of these methods to identify and analyze SNP genotypes of genes other than blood group antigen and HPA.

Claim 24 is indefinite, broader in scope than the teaching of the description and do not comply with Article 6 of the PCT. The expression "or any other antigen for which a SNP has been identified" lacks clarity. The other antigen is not defined. Also, the applicant has not use the method as claimed in claim 14 to analyze other antigen SNPs than the ones already listed in the present claim.

Claim 27 is ambiguous and does not comply with Article 6 of the PCT. The term "the HPA-1 GP3A SNP" has no antecedent basis in claim 14.

Claims 28 and 29 are indefinite, broader in scope than the teaching of the description and do not comply with Article 6 of the PCT. Applicant is claiming a method without fully defining it in the claims. A method is a series of steps to be followed to achieve a desired result. All of the essential steps of the allegedly novel method must be defined. Also, the applicant has not disclosed methods to identify blood group SNPs other than the one described in claim 14, where a multiplex PCR amplification step, a digestion step, a single-base pair primer extension step, an hybridization step and an analysis step are comprised in the method.

Claim 34 is indefinite and does not comply with Article 6 of the PCT. The expression "analysis thereof" is vague and ambiguous. It is not clear what is meant exactly by this expression.

Claims 36, 38 and 39 are indefinite and do not comply with Article 6 of the PCT. The word "preferably" lacks clarity and renders the scope of the claims ambiguous.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

Document D3 discloses methods of allele-specific primer extension useful for detecting mutations and genetic variations. Human genomic DNA is isolated, then, multiplex PCR was performed to amplify multiple single nucleotide polymorphisms. The SNPs were wiaf1764 (A/C) on chromosome 9q, codon 72 (C/G) on the p53 gene, nucleotide position 677 (C/T) on the MTHFR gene and nucleotide position 196 (A/G) on the GPIIIa gene. After multiplex PCR, primer extension reactions are performed using labelled nucleotides in the presence of a nucleotide-degrading enzyme. The teaching of this reference falls within the scope of claims 29 to 33, 41 and 45. Therefore, these claims do not comply with Article 33(2) of the PCT in view of D3.

Document D4 discloses a primer extension method to identify polymorphisms of the Duffy blood group. This document teaches that multiple sites are investigated by simultaneously amplifying multiple regions of the nucleic acid sets of allele-specific primers (see page 19). The method described in this document falls within the scope of claims 29 to 32. Therefore, these claims do not comply with Article 33(2) of the PCT in view of D4.

Document D5 discloses a method for parallel genotyping of SNPs, called single base extension-tag array on glass slides, SBE-TAGS. This method comprises the steps of isolating genomic DNA, multiplex PCR, the multiplex amplified products are digested by shrimp alkaline phosphatase and exonuclease I, the PCR products are treated with a single base extension (SBE) mix containing tag-single base extension primers, the SBE products are added to the microarray for hybridization and then, the array is analyzed to determine the SNP genotypes. The teaching of this reference falls within the scope of claims 33 and 41. Therefore, these claims do not comply with Article 33(2) of the PCT in view of D5.

Document D6 discloses a method of genotyping HPA-1. This method comprises amplification of the polymorphic region followed by restriction enzyme analysis or amplification with sequence-specific primers. This method is based on the single nucleotide extension of a primer, which is designed to anneal directly adjacent to the base of interest. The HPA-1 genotype of 50 unselected patients was determined. Also, this method is used for multiplex determination of several mutations in the same reaction. The teaching of this reference falls within the scope of claims 29 to 32. Therefore, these claims do not comply with Article 33(2) of the PCT in view of D6.

Document D7 disclose a DNA-based PCR method for the detection of two RH genes and their alleles, including variant RHD alleles, was developed. The DNA of 77 blood donors carrying weak D and that of 200 random donors with common D phenotypes was investigated. In addition, 77 selected samples of ccDee and rare Rh system phenotypes were examined. The teaching of this reference falls within the scope of claim 28. Therefore, claim 28 does not comply with Article 33(2) of the PCT in view of D7.

INVENTIVE STEP:

As claims 1 to 5, 8 to 12, 28 to 33, 40 to 42 and 45 have been found to lack novelty under Article 33(2) of the PCT, they also lack an inventive step under Article 33(3) of the PCT.

It is obvious to a skilled person, in view of D3 and common general knowledge, to prepare other primers directed to other blood group antigens in the method to identify blood group SNPs as taught in D3. Therefore, claims 1 to 14, 16 to 25, 27, 34 to 40, 42 to 44 do not define an inventive step under Article 33(3) of the PCT in view of document D3 and common general knowledge.

Also, it is obvious to a skilled person and in view of the common general knowledge to prepare primers directed to blood group antigen DNAs or HPA DNAs and use them in the SBE-TAGS method as described in D5 to identify SNPs of blood group antigens as described in D4 and D7or human platelet antigen as taught in D6. Therefore, claims 1 to 27, 34 to 40 and 42 to 45 do not define an inventive step under Article 33(3) of the PCT in view of the common general knowledge and documents D4, D5, D6 and D7.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

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INDUSTRIAL APPLICABILITY:

Claims 1 to 45 appear to have industrial applicability under Article 33(4) of the PCT, based on the use of the primers and probes of Tables 1 and 2 in a method of simultaneously analyzing a plurality of blood group or HPA antigens in a sample.